DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
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[December 9, 2003]

TO: Cristina V. Beato, M.D.
Acting Assistant Secretary for Health

FROM: Acting Director, Office for Human Research Protections

SUBJECT: Deferral of HHS Support for Research–ACTION

ISSUE

Recommendation by the Office for Human Research Protections (OHRP) that the Department of Health and Human Services (HHS) defer supporting the proposed research protocol entitled "Alcohol, Sleep and Circadian Rhythms in Young Humans: Study 2 – Effects of Evening Ingestion of Alcohol on Sleep, Circadian Phase and Performance as a Function of Parental History of Alcohol Abuse/Dependence" involving the enrollment of 15- to 16-year-old subjects. In making this recommendation, OHRP has reviewed the proposed research and considered the opinions of experts as well as comments received from the public, in accordance with 45 CFR 46.407.

DISCUSSION

Background: All studies conducted or supported by HHS that are not otherwise exempt and that propose to involve children as research subjects require institutional review board (IRB) review in accordance with the provisions of HHS regulations at 45 CFR part 46, subpart D. Pursuant to HHS regulations at 45 CFR 46.407, if an IRB reviewing a protocol to be conducted or supported by HHS does not believe that the proposed research involving children as subjects meets the requirements of HHS regulations at 45 CFR 46.404 (research not involving greater than minimal risk), 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects), or 46.406 (research involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition), and was suitable for review under the procedure provided in 45 CFR 46.407 (research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children), the research may proceed only if the following conditions are met: (a) the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and (b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity

for public review and comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR
46.404, 46.405, or 46.406, or (2) that the following conditions are met: (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) the research will be conducted in accordance with sound ethical principles; and (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

In May 2001, OHRP received a request from the Lifespan Office of Research Administration, Rhode Island Hospital, to review the above-cited protocol pursuant to requirements of HHS regulations for the protection of human subjects at 45 CFR 46.407. The proposed research would be supported by National Institutes of Health (NIH) grant 1 R01AA1352-0 awarded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). After reviewing the proposed research, the Rhode Island Hospital IRB determined that it could not approve this study under HHS regulations at 45 CFR 46.404, 46.405, or 46.406, but found the research presented a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children and was suitable for review under 45 CFR 46.407. The research protocol is proposed to take place at E. P. Bradley Hospital, East Providence, Rhode Island, and was reviewed by the Rhode Island Hospital IRB which is the IRB of record for E. P. Bradley Hospital

In its initial request for review pursuant to 45 CFR 46.407, the Rhode Island Hospital submitted two studies under the larger grant: (1) Study 2 which proposed to study the effects of a small or moderate evening dose of alcohol on sleep, waking performance, and circadian phase in a total of 32 adolescents (15 to 16 years of age) and 32 young adults (21 to 22 years of age), and examine how the effects may differ between individuals who have a parent with a history of alcohol dependence and those who do not; and (2) Study 3, "Effects of Circadian Phase and Sleep/Wake Homeostasis on Alcohol's Effects on Sleep, Performance, Sleepiness, and Mood." Study 3 proposed to alter normal sleep patterns and administer a small or moderate evening dose of alcohol to 24 subjects 18 to 22 years old, in order to study effects of alcohol on the circadian timing mechanism and sleep/wake homeostatic process. (See Tab A - Clinical Trial Outline). Since the initial submission of these studies for review under 46.407, OHRP determined that Study 3 was not eligible for review under the provisions of 45 CFR 46.407 because it involved subjects 18 to 22 years of age and did not involve "children" as defined by HHS regulations and Rhode Island state law. In addition, the Rhode Island Hospital IRB has reviewed and approved amendments to the original protocols, approving Study 3 as well as that portion of Study 2 involving subjects 21 years of age or older. For this reason, a decision by HHS under 46.407 on whether to support the proposed research is focused on that portion of Study 2 involving subjects 15 to 16 years of age.

Review by HHS Panel of Experts: In August 2001 OHRP assembled a panel of experts in accordance with the provisions of HHS regulations at 45 CFR 46.407, and each provided his/her recommendation to the Secretary (See Tab B - Tabular Summary of Expert Recommendations). The experts' areas of

expertise included ethics, pediatrics, sleep medicine, psychiatry, and

epidemiology. All experts, as individually expressed in their reports, indicated that the research was approvable under 45 CFR 46.407, presenting a reasonable opportunity to understand a serious problem (alcohol abuse) affecting the health and welfare of adolescent children. In general, the experts found that the research was not likely to directly benefit the individual subjects. All experts stated that the research constituted more than minimal risk to the research subjects, with six experts indicating that they considered the risk to be a minor increase over minimal risk. Some experts noted that those subjects with a positive family history of alcohol abuse or alcoholism could be considered to have a disorder or condition, and therefore, for those subjects, the research could be approved under 45 CFR 46.406.

While all experts, as individually expressed, found that the protocol could be approved under 45 CFR 46.407, several experts recommended specific modifications to the assent/parental permission/consent documents [hereafter referred to as consent documents]. The recommended revisions to the consent documents included (1) providing a clearer statement that there was no direct benefits to individual subjects; (2) avoiding the implication that the certificate of confidentiality provides more protection than is actually afforded; and (3) the amount of alcohol administered in the placebo dose (i.e., "few drops") should be quantitated in milliliters.

Public Review and Comment: On April 14, 2003, a *Federal Register* Notice was published soliciting public review and comment, pursuant to the requirements of 45 CFR 46.407, for a period of 45 days. Documents related to the protocol were made available on the OHRP website, including the grant proposal, IRB protocol application, assent/consent/permission documents, IRB deliberations on the proposed protocol, and OHRP's January 13, 2003 letter to the principal investigator explaining why review pursuant to 46.407 was restricted to Study 2.

A total of 36 comments were received (see Tab C - Tabular Summary of Public Comments). Twenty-six commenters stated that the research proposal should be approved, nine commenters felt that the research should not be approved, and one commenter did not specify his recommendation.

Twenty-five of the 26 commenters recommending approval were from academic institutions; most of those recommending approval identified their expertise in sleep research. Others recommending approval identified their expertise in psychiatry, psychology, neurology. One of the commenters who recommended approval identified himself as a federally funded researcher conducting intervention studies on the treatment of adolescent substance use problems. Several commenters recommending approval cited the credentials of the researchers and the research's strong scientific underpinnings, and the benefits to society to be derived from knowledge gained. Three academicians recommending approval provided the following recommendation: "I urge the Secretary of Health and Human Services to support Dr. Carskadon's work, and to ensure the proper oversight of the study with a Data Safety Monitoring Board."

The nine commenters recommending disapproval included (1) a health statistician on the HRSA Human Subjects Committee, (2) an administrative assistant from a pharmaceutical company, (3) a sleep researcher and associate professor; (4-6) the executive director of an "international on-line Fetal Alcohol Spectrum Disorders information, support and discussion forum" and two participants in the on-line forum; (7) an associate director of a "County Policy Panel on Youth Access to Access"; (8) an individual with family history of alcoholism; and (9) the executive director of the Rush Recovery Institute, an alcohol abuse treatment center. The individuals recommending disapproval expressed concern about administering alcohol to underage drinkers as part of the research protocol, including the potential long term consequences of developing alcoholism, particularly in those subjects with a family history of alcoholism. One commenter who was a sleep researcher argued that there is "no compelling reason to extend this research to children in whom alcohol use is proscribed by society."

NIAAA Special Emphasis Panel: During the review under 46.407 of the proposed research, OHRP considered the report of the NIAAA Special Emphasis Panel, the peer-review committee convened in October/November 2000 to review the original grant application. According to the report, the "committee considered this an outstanding proposal that addresses a significantly important research topic . . . The design is hypotheses driven, highly innovative and has the potential to result in new insights into the sedative effects of alcohol especially in young people." In particular, the committee considered the issues related to Studies 2 and 3 and the plan to administer alcohol to 15- to 16-year-old subjects. The committee concluded that "[a]lthough the scientific merit of the proposed work is outstanding, it was recommended that studies 2 and 3 be delayed until the human subjects issues are resolved as detailed later in the HUMAN SUBJECTS section."

The HUMAN SUBJECTS section of the Special Emphasis Panel report included the following concerns and recommendations: (1) the investigators must establish medical oversight for their subjects beyond the simple performance of paid physical examinations and emergency backup procedures; (2) the investigators should first conduct alcohol administration studies with the sleep protocol in young adult subjects before seeking approval to conduct the protocol with adolescents; (3) the investigators should detail how they will handle subjects who try to leave the sleep unit prematurely after drinking alcohol; (4) a blood test, rather than a urine test, should be used to screen for pregnancy of female subjects because of improved accuracy; (5) the investigators should justify the $640 payments to the subjects in Study 2.

On February 6, 2001, Dr. Mary Carskadon, the principal investigator, responded to the human subject concerns outlined above. Specifically, Dr. Carskadon outlined plans to improve medical coverage by appointing a Dr. Robert Swift, a researcher in alcohol and addiction as ongoing medical consultant to the investigators and research team. An accompanying letter by Dr. Swift detailed his participation as consultant but indicated that he was "unable to sign on as physician of record for [Dr. Carskadon's] project; but formal time constraints make that role impossible." The principal investigator explained that enrollment of 15- to 16-year-old subjects at the same

time as adult subjects within Study 2 was necessary to preserve scientific validity of the study and to avoid cohort effects in collecting the data. She described procedures and safeguards for handing subjects who do not comply with the protocol, revised the protocol to use a blood test for pregnancy; and explained the formula for compensating study subjects.

In April 2003, at the request of the Rhode Island Hospital IRB, Dr. Carskadon submitted to the IRB a brief "Data and Safety Monitoring Plan." Such a plan is required under NIH and NIAAA guidelines (see http: //www.niaaa.nih.gov/extramural/guidance.htm). Under this plan, the principal investigator and Dr. Gregory Fritz, Professor of Psychiatry and Human Behavior, will review patient safety data on a semiannual basis to examine trends and prepare a brief annual report in order to ensure that patient risks are monitored and minimized. Specifically, the PI and Dr. Fritz will provide oversight of (1) monitoring the safety of participants; (2) maintaining the confidentiality and integrity of the data; (3) receiving/eliciting reports of critical or adverse events from research staff on an event by event basis; (4) reporting of an adverse event to co-investigators, the Rhode Island Hospital IRB, and the Program Officer at NIH.

OHRP RECOMMENDATION:

OHRP has reviewed the research protocol and considered the recommendations provided by the experts, comments received from the public, and the deliberations of the NIAAA Special Emphasis Panel. OHRP recommends that HHS defer support of the proposed research protocol involving the enrollment of 15- to 16-year-old subjects until the completion of ongoing IRB-approved studies under grant 1 R01 AA13252 involving the administration of alcohol to subjects 18 years of age or older, and analysis of the resulting data.

OHRP bases its recommendation on the reports of experts who have reviewed this research protocol under 45 CFR 46.407, comments received during the public review and comment period, as well as the comments of the NIAAA Special Emphasis Panel which reviewed the initial grant application. OHRP finds that the research is not approvable under 45 CFR 46.404 because the research involves administration of moderate amounts of alcohol to minor subjects which constitute greater than minimal risk to the subjects. OHRP finds that the research may not be approved under 45 CFR 46.405 because the proposed protocol involves healthy children, who are unlikely to directly benefit from participation in this research. Because the subjects to be enrolled in this study include healthy children who do not have a disorder or condition, OHRP finds that this research may not be approved under 45 CFR 46.406.

OHRP has determined that the research protocol does not reach the threshold required for approval under the provisions set forth in HHS regulations at 45 CFR 46.407 which require that the research (i) present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) be conducted in accordance with sound ethical principles; and (iii) have adequate provisions for soliciting the assent of children and the permission of

their parents or guardians, as set forth in 45 CFR 46.408.
OHRP feels that the research under grant 1 R01 AA13252 addresses a fundamentally important topic, namely the interactions between sleep and alcohol use, intended to provide insights into the prevention and treatment of alcohol abuse which is a serious problem affecting the health and welfare of adolescents and young adults. However, OHRP is recommending that HHS defer support for the proposed research involving the enrollment of 15- to 16-year-old subjects in Study 2, despite the experts' recommendations and public comments supporting this research, because of concerns outlined below.

In determining whether the research would be conducted in accordance with sound ethical principles, OHRP has considered the relevant requirements set forth in 45 CFR 46, subpart A. HHS regulations at 45 CFR 46.111(a)(3) require an IRB to determine that the selection of research subjects be equitable and that the research setting be particularly cognizant of the special problems of research involving vulnerable populations, including children. In addition, 45 CFR 46.111(b) requires an IRB to determine that "when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children . . . or economically or educationally disadvantaged persons . . . additional safeguards have been included in the study to protect the rights and welfare of these subjects." Of particular relevance to the proposed research is the NIAAA National Advisory Council on Alcohol Abuse and Alcoholism's Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation which states that "the principles for all research with children dictate that the research first begin with animals or adults before involving children." [available at http://www.niaaa.nih.gov/extramural/job22.htm.].

In the IRB deliberations on the original protocol, the principal investigator acknowledges that this type of research has not been performed previously in children. In addition, the principal investigator, in the study protocol and assent/permission/consent documents, acknowledges the unknown risk for study subjects of later developing alcohol abuse/dependence, especially for those subjects with a family history of alcoholism. The research protocol has incorporated several procedures to minimize risk including (1) limiting enrollment of subjects to those with a past history of moderate alcohol use and excluding subjects with a history of alcohol abuse; (2) consulting with an expert on alcohol and addiction medicine in the study design and medical monitoring of subjects; and (3) adding a data monitoring plan to provide for a semiannual review of subject safety data. However, the proposed research involves 15- to 16- year-old children who have admitted to high risk behavior (i.e., consumption of moderate amounts of alcohol). A body of literature has emerged, linking early drinking with subsequent development of alcohol abuse and dependence. For example, studies have found that youth who drink before the age of 15 are more likely to develop alcohol dependence than those who begin drinking at age 21 (NIAAA 1997; Grant 1998). Studies have also demonstrated an association between drinking before the age of 15 and a range of high risk behaviors such as driving after drinking, illicit drug use and dependence, underachievement in school, and alcohol-related injuries (McGee et al 2001; Hingson et al 2003). In the proposed research protocol, some subjects will be recruited through solicitation of parents who are in alcohol treatment centers, and therefore may be vulnerable by virtue of

being children of individuals with a history of alcohol or substance abuse (Biederman et

al 2000). For these reasons, OHRP remains concerned regarding the particular vulnerability of 15- to 16-year-old subjects, one half of whom have a parental history of alcohol dependence.

Under HHS regulations at 45 CFR 46.111(a)(1)(i), an IRB must ensure that risks to subjects are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risk. According to 45.CFR 46.111(a)(6) an IRB must determine that, when appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects. The current protocol does not have a dedicated medical monitor to ensure overall medical oversight of the individual study subjects, but rather depends upon multiple individuals over the course of the study to perform medical screening exams, medical backup during alcohol administration and sleep studies, and to review adverse events. The current protocol does not monitor subjects following completion of the final in-lab sleep study, and therefore does not assess whether or not participation had adverse consequences to the individual study subject, either in the short or long term. While the protocol includes a motivational interview following the completion of the in-lab study, no details are provided within the protocol regarding the content of this interview in order to assess the merits of this procedure.

HHS regulations at 45 CFR 46.111(a)(2) require that an IRB must determine that risks are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of knowledge that may reasonably be expected to result. OHRP finds that adequate justification has not been provided to proceed with the proposed protocol involving 15- to 16-year-old subjects that will present more than minimal risk without the prospect of direct benefit. OHRP notes that ongoing IRB-approved studies under the grant will provide data relevant to both the safety of study subjects and the scientific rationale for involving 15- to 16-year-old subjects. Upon completion of Dr. Carskadon's ongoing research on adults under the grant 1 R01 AA132, "Alcohol, Sleep and Circadian Rhythms in Young Humans," and analysis of its data, re-review of the proposed research would be warranted to consider extending the research to 15- to 16-year-old subjects.

Finally, concerns were raised by HHS officials in discussions with OHRP that the protocol did not control for the potential confounding affects of smoking in both male and female subjects and endocrine changes over the course of the menstrual cycle in the female subjects on the study outcome measures.

Regarding ongoing IRB-approved studies under grant 1 R01AA13252, OHRP intends to offer the following guidance:

(1) The investigators should consider the appointment of a dedicated medical monitor with overall medical oversight for research subjects during the course of the study. It is recommended that this physician be made part of the investigator team and key personnel. In addition to medically clearing the subject for participation in Study 2, the individual
would serve as the physician of record during the inpatient alcohol administration studies, and during the follow up of study subjects (see item 2 below). Ideally, this individual would possess experience or certification in addiction medicine.

(2) The investigators should consider incorporating into the experimental protocol a procedure for

the medical and psychological follow up of subjects at a defined interval(s) subsequent to the final in-lab study visit. These procedures are intended to assess effects, if any, of study participation on subsequent alcohol or substance use by individual research subjects, and to ensure appropriate medical, psychological, or substance abuse referral.

(3) The investigators should consider revising the assent/permission/consent documents:

(a) To state more clearly that the study is not likely to present the prospect of direct benefits to individual subjects;
(b) To avoid implying that the Certificate of Confidentiality may provide more protection than is actually afforded; and
(c) To clearly state the specific amount of alcohol administered in the placebo dose (in milliliters).

(4) The investigators should reconsider the compensation scheme for study subjects to avoid a bonus provided only upon study completion. OHRP is concerned study subjects may feel pressure to complete the alcohol administration study despite experiencing unpleasant side effects from study participation.

References:

Biederman J, Faraone SV, Monuteaux MC, Feigner JA. Patterns of alcohol and drug use in adolescents can be predicted by parental substance use disorders. *Pediatrics* 2000;106):792-7.

Grant BF, Dawson DA. Age at onset of alcohol use and association with DMS-IV alcohol abuse and dependence: Results from the National Longitudinal Alcohol Epidemiological Survey. *Journal of Substance Abuse* 1997; 9:103-110.

Hingson RW, Heeren T, Jamanka A, Howland J. Age of drinking onset and unintentional injury involvement after drinking. *JAMA* 2000; 284:1527-33.

McCue M, Iacano WG, Legrand LN, Malone S, Elkin I. Origins and consequences of age at first drink. *Alcohol Clin Exp Res* 2001; 25:1156-65.

NIAAA - National Institute on Alcohol Abuse and Alcoholism, National Advisory Council on Alcohol Abuse and Alcoholism's *Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation*," revised in June 1989, available at http://www.niaaa.nih.gov/extramural/job22.htm.

NIAAA - National Institute on Alcohol Abuse and Alcoholism, Washington, D.C. Alcohol Alert No. 35, PH 371, January 1997.

RECOMMENDATIONS

1. Determine that HHS should defer support of the proposed research protocol, Study 2, involving the enrollment of 15- to 16-year-old subjects.

2. Make this decision available to the public via appropriate methods, such as placement on the OHRP web site.

DECISION

1. Determine that HHS should defer support of the proposed research protocol, Study 2, involving the enrollment of 15- to 16-year-old subjects.

Approved /s/ Cristina V. Beato, M.D. Disapproved _____ Date [Dec.12, 2003]

2. Make this decision available to the public via appropriate methods, such as placement on the OHRP web site.

Approved /s/ Cristina V. Beato, M.D. Disapproved _____ Date [Dec.12, 2003]

/s/ Bernard A. Schwetz

Bernard A. Schwetz, D.V.M., Ph.D.

3 Attachments:
Tab A - Clinical Trial Outline
Tab B -Tabular Summary of Experts' Recommendations
Tab C -Tabular Summary of Public Comments